From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Rec'd PCT/PTO 14 MAR 2005

DUE DATE: 14 Mai 2005
by:

PCT

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WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	25.08.2004
Applicant's or agent's file reference: 114-175PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/01331	12.09.2003	13.09.2002

International Patent Classification (IPC) or both national classification and IPC
C07D335/20

Applicant
PRESCIENT NEUROPHARMA INC. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 13.01.2005

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-58 as originally filed

Claims, Numbers

1-18 as originally filed

Drawings, Sheets

1/13-13/13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 5-18 with respect to IA

   because:

   ☒ the said international application, or the said claims Nos. 5-18 with respect to IA relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9 (all part; subject-matter relating to X=S), 10-20 (all complete) .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	Yes: 1-12,14-18; No: 13
Inventive step (IS)	Claims	No: 1-18
Industrial applicability (IA)	Claims	1-4

2. Citations and explanations

see separate sheet

1. **Re Item I** ***(Basis of the report)***

Reference is made to the following documents:

D1: WO 99/54280 A (CAN.) 28 October 1999 (1999-10-28)

D2: PELLICCIARI R ET AL: "Synthesis and preliminary evaluation of (S)-2-(4'-carboxycubyl)glyci ne, a new selective mGluR1 antagonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 12, 16 June 1998 (1998-06-16), pages 1569-1574, XP004137086 ISSN: 0960-894X

2. **Re Item III** ***(Non-establishment of opinion with regard to novelty, inventive step and industrial applicability)***

2.1 For the assessment of the present claims 5-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.2 In receipt of an invitation to pay additional fees or to restrict in view of non-unity of the present application (see point 3 below), the Applicant paid an additional fee for the subject-matter of Group 5. Accordingly, no opinion is established for subject-matter relating to compounds of formula I wherein X is O, NH, S=O or $S=O_2$ (subject-matter of claims 1-9 in part).

3. **Re Item IV** ***(Lack of unity of invention)***

The use of disclaimers or provisos in order to establish novelty of the to be claimed subject-matter over prior art may render the subject-matter of the application in suit non-unitary, since structures exhibiting the same activity may be excluded by those disclaimers or provisos. All inventions claimed in the same patent application shall involve at least one special technical feature.

In the present case, thioxanthines according to compound 6 of D1 are known having the same biological activity (see D1, page 15-19). Accordingly, neither common **structural** feature nor a common feature relating to a particular **activity** of the compounds of claim 1 is apparent which represents a contribution over the prior art and which would render the subject-matter of claim 1 unitary.

Furthermore, since the specific technical feature of claims 10-20 appears to be represented by the **prophylactic activity** of the compounds described, unity among the subject-matter of claims 1-9 on the one hand and claims 10-20 on the other hand is not apparent.
Accordingly, the IPEA found the following five inventions in this international application:

Group 1: Claims 1-9 (all part), 13
subject-matter related to compounds wherein **X is S**

Group 2: Claims 1-9 (all part)
subject-matter related to compounds wherein **X is O**

Group 3: Claims 1-9 (all part)
subject-matter related to compounds wherein **X is NH**

Group 4: Claims 1-9 (all part)
subject-matter related to compounds wherein **X is S=O or $S=O_2$**

Group 5: Claims 10-12 and 14-18
subject-matter related to a **prophylactic activity**

4. Re Item V *(Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement)*

4.1 Subject-matter

The present application discloses in claim 1 xanthenyl cubane derivatives as agonists of antagonists at certain metabotropic glutamate receptors being useful in the treatment of neurological disorders.
Claims 10-20 disclose these compounds in the prevention of the said diseases.

4.2 Novelty

4.2a Group 1 (claims 1-9 (all part), 13)

Document D1 discloses in claim 1 cubane derivatives characterized by R_3 being

H, aliphatic, aromatic or heterocyclic. In particular, example 3 of D1 discloses a thioxanthenyl derivative (see compound 6).

The subject-matter of claims 1-9 differs from D1 in view of the proviso of claim 1 excluding compound 6 of D1.

The subject-matter of claim 13 is not novel in view of D1 (see figure 1; see paragraph bridging pages 18 and 19; see claim 7).

The subject-matter of claims 1-9 and 13 differs from D2 in present R_3.

The requirements of Art. 33(2) PCT are not fulfilled since claim 13 is not novel over D1.

4.2b Group 5 (claims 10-12 and 14-18)

The subject-matter of Group 5 differs from D1 and D2 in view of the **prophylactic** use.

4.3 Inventive step

Document D1 is considered as closest prior art. This document discloses cubane derivatives as agonists or antagonists of the metabotropic glutamate receptor system being useful in the treatment of diseases of the central nervous system.

4.3a Group 1 (claims 1-9 (all part), 13)

Until claims have been received which satisfy Art. 33(2)PCT, a final decision on the inventive step of the present application cannot be taken.
However, the following observations may be pointed out:

In view of this document, the problem to be solved can be regarded as the provision of further compounds exhibiting the same activity as D1.

The solution to this problem consists in compounds according to claim 1.

However, the problem is at present not considered as being solved in view of the fact that the results presented on pages 53-58 relate to compound 6 with is excluded by the proviso of claim 1. Accordingly, it has not been shown that the claimed alternatives to this compound (already known from D1 for the same

purpose) exhibit the alleged activity.

In addition, the subject-matter of present claim 1 is considered as a selection in view of present R_3 over the generic disclosure of D1. Such a selection can only be regarded as inventive, if the claimed selection presents unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application, in particular in comparison to compound 6 of D1 which represents the closest approximation.

Hence, no inventive step is present in the subject-matter of claims 1-9 and 13.

4.3b Group 5 (claims 10-12 and 14-18)

In view of D1, the problem to be solved can be regarded in the provision of further compounds having an unexpected effect/use.

The solution consists in compounds according to claim 10-12 and 18-20 for the prophylaxis of central nervous diseases.

Neuroprotective effects have been shown in examples 3 and 4 of the specification.

This solution is considered as obvious since thioxanthenyl derivatives of cubanes are already known from D1 having a CNS activity based on antagonizing and/or agonizing metabotropic glutamate receptors. Since it is known that mGluRs have therapeutic potential for the treatment of neurological disorders, the man skilled in the art would not be surprised starting from D1 that the compounds of the present invention exhibit prophylactic activity. D1 e.g. discloses that mGluRs protect nerve cells from excitotoxic damage resulting from ischemia, hypoglycaemia and anoxia (see D1, page 4, first paragraph).

Hence, no inventive step is present in the subject-matter of claims 10-12 and 14-18.

4.4 Industrial applicability

For the assessment of the present claims 5-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.5 Further matters

a) The claim numbers 17 and 18 appear twice. The set of claims should be renumbered accordingly.

b) Claims 10 and 12 appear to be identical thereby leading to a lack of conciseness.